Myocardial Contractile Reserve Accurately Predicts Positive Response to Cardiac Resynchronization Therapy

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Abstract

Background- Up to 30% of patients with heart failure fail to respond to cardiac resynchronization therapy. This study was aimed at assessing the role of low-dose dobutamine stress echocardiography along with tissue Doppler imaging indices to predict response to cardiac resynchronization therapy.

Methods- Twenty-one consecutive patients with systolic heart failure who were candidates for cardiac resynchronization therapy were prospectively included. Contractile reserve was assessed by low-dose dobutamine stress echocardiography (cut-off: 5 and 10%). Interventricular and intraventricular dyssynchrony (using 6 basal, 6 mid-segmental models) was assessed. Acute post-cardiac resynchronization therapy response was defined by 15% or more decrease in the left ventricular end systolic volume. Sensitivity, specificity, predictive values, and likelihood ratios were calculated for the tests singly and in combination.

Results- Low-dose dobutamine stress echocardiography had the highest specificity (80%) and positive likelihood ratio (2.5), but interventricular dyssynchrony exhibited the highest sensitivity (83.3%) and the lowest negative likelihood ratio (0.4) for predicting positive response to CRT.

Conclusion- Inotropic contractile reserve assessed by low-dose dobutamine stress echocardiography strongly predicts acute response to cardiac resynchronization therapy ***(Iranian Heart Journal 2010; 11 (3): 29-36).***

Key words: heart failure ■ dyssynchrony ■ cardiac resynchronization therapy ■ stress echocardiography ■ contractile reserve

Cardiac resynchronization therapy (CRT) is a valuable adjuvant therapy for patients with refractory congestive heart failure (CHF).[1] Previous studies have shown that CRT can improve the clinical symptoms, exercise capacity, quality of life, and survival of these patients mainly through restoring ventricular function by timely pacing both ventricles.[2-4] A considerable proportion of patients who receive CRT on the basis of the current criteria do not experience a full response.[1-5] Thus, considering its invasive nature, identification of potential responders to CRT before implantation of the pacemaker seems to be crucial.[1] A variety of methods have been studied and several parameters proposed as the predictors of responsiveness.[6] Among them, echocardiographic assessment of ventricular dyssynchrony carried out

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mainly through Doppler tissue imaging (DTI) showed to provide the most promising prediction.[7-10]

Nevertheless, further studies revealed that a substantial number of patients do not benefit form CRT despite the presence of ventricular dyssynchrony, making prospective identification of potential responders even more challenging. It has been recently hypothesized that the low likelihood of response may be due to the presence of scar tissue, which can negatively influence the myocardial contractility and conduction properties or the absence of adequate inotropic contractile reserve.[11] Dobutamine stress echocardiography (DSE), which serves as an efficient non-invasive technique for assessing myocardial viability and contractile reserve,[12,13] has shown to have predictive value in distinguishing responders to CRT.[11,14,15] The aim of this study was to investigate the role of DSE singly and in combination with other techniques in predicting CHF patients' response to CRT.

Methods

Study populations

From January 2007 to December 2007, twenty-one consecutive CHF patients scheduled for CRT who met the inclusion criteria were prospectively enrolled into the study. Patients were eligible for the study if they had NYHA functional class III/IV heart failure despite optimal medical therapy, impaired left ventricular ejection fraction (LVEF<35%), and QRS duration >120 milliseconds with left bundle branch block (LBBB) pattern or intraventricular conduction delay (IVCD). Exclusion criteria were: 1) hypertrophic or restrictive cardiomyopathy, 2) acute coronary syndrome, 3) correctable valvulopathy, and 4) planned revascularization.

Study protocol

All the participants underwent a clinical examination, 12-lead electrocardiography (ECG), 2-D echocardiography with color Doppler study, DTI, and low-dose DSE at baseline, before receiving the implant. All these measures, apart from DSE, were repeated for the entire participants three days after the implantation of a cardiac resynchronization device in order to assess the outcome. The institutional review board of the hospital approved the study protocol, and all the patients gave written informed consent.

Echocardiography measures

Standard transthoracic two-dimensional (2D) and color Doppler echocardiography were performed at baseline and three days after CRT by two experienced observers, who were blinded to the patients' status and the clinical data. The patients were imaged in the left lateral decubitus position using a commercially available system (Vivid 7; General Electric Company, Norway) equipped with a M3S transducer in the parasternal and apical views.

The left ventricular (LV) volumes and the left ventricular ejection fraction (LVEF) were measured by averaging three measurements in the apical two- and four-chamber views using modified Simpson's rule. Right ventricle (RV) size and function were computed by averaging three measurements in the apical four-chamber view. The pressure gradient between the right ventricle and right atrium during systole was calculated using the simplified Bernoulli equation. Diastolic dysfunction was evaluated by mitral valve inflow velocities, mitral annular velocity, pulmonary vein flow, and velocity of propagation. Mitral regurgitation (MR) was assessed by qualitative and quantitative parameters for grading MR based on the American Society of Echocardiography guidelines

Interventricular dyssynchrony

Interventricular dyssynchrony was assessed by comparing the aortic and pulmonary valve pre-ejection times. The pre-ejection time was measured with pulse-wave Doppler echocardiography from the onset of the QRS complex on the ECG to the onset of aortic or pulmonic flow. A cut-off value of 40 milliseconds was used for the identification of possible responders.

Intraventricular Dyssynchrony

For the echocardiographic assessment of intraventricular dyssynchrony, pulsed wave TDI spectral recordings and TSI method were used to determine the timing of systolic myocardial velocities as follows: 1) the maximum difference in time-to-peak systolic velocities segments among 12 segments (TS-diff), 2) septum-to-lateral wall mechanical delay, and 3) total asynchrony index (the standard deviation of the time-to-peak systolic velocity of 6 basal and 6 middle LV segments). The cut-off values for predicting the possible response to CRT were defined as 100, 60, and 33 milliseconds for the tests respectively, based on the American Society of Echocardiography guidelines.

Myocardial viability: low-dose dobutamine stress echocardiography

After obtaining the baseline echocardiographic data, stepwise infusion of dobutamine was performed for all the patients. Dobutamine was initiated at the rate of 2.5µg/kg/min and continued in three-minute dose increments of 2.5 to 15 µg/kg/min. The echocardiographic measures were recorded and averaged from the apical two- and four-chamber views. Using the biplane disk method, LV end diastolic and end systolic volumes were measured off-line at rest at each dobutamine level. The LVEF values were recorded as the average of three consecutive beats. Positive inotropic contractile reserve was defined by two cut-off values: the first as 5% or more and the second as 10% or more increase in LVEF during low-dose DSE before receiving CRT.

Pacemaker implantation

After obtaining the baseline evaluations, the patients underwent implantation of a cardiac resynchronization device (InSync model 8040, Medtronic and Frontier II model 5596 St. Jude) along with three pacing leads: a standard right atrial lead, a specialized left ventricular lead, and a standard right ventricular lead. The three leads were inserted transvenously via the subclavian route. The atrial lead was positioned in the high right atrium. The left ventricular pacing lead was placed in a tributary of the coronary sinus. The preferred sites were lateral and posterolateral, although posterior placement of the lead was also considered as an acceptable alternative. The right ventricular lead was positioned at the farthest possible site from the left ventricular lead. Adequate pacing and sensing properties of all the leads were tested. Acute post-CRT response, measured three days after CRT, was defined as 15% or more decrease in the left ventricular end systolic volume (LVESV) in comparison with the baseline measures.

Statistical analysis

The continuous variables are presented as mean± standard deviations (SD), and the categorical data are expressed as frequencies and proportions. The sensitivity (Sn), specificity (Sp), positive likelihood ratio (PLR), and negative likelihood ratio (NLR) of inter- and intraventricular dyssynchrony and DSE for the identification of the potential responders to CRT were calculated by using acute post-CRT response seen three days following implantation. Positive and negative predictive values were also computed accordingly. Furthermore, 95% confidence interval for LRs was computed. Possible combinations of inter and intraventricular dyssynchrony and DSE were considered to achieve the best predictor of the early outcome, which was defined as 15% or more decrease in LVESV as compared to the baseline. All the statistical analyses were performed using SPSS-13 (Chicago, IL, USA) for Windows.

Results

The baseline characteristics of the participants are summarized in Table I. All the 21 patients who had met the entry criteria completed the study protocol (including CRT device implantation) without complications. Six (29%) participants experienced an increase of over 5% in LVEF during low-dose DSE, and three (14%) had LVEF increase of more than 10 % (Table II).

Table I. Baseline characteristics of the patients

Study Population	(n=38)*
Age (year)	57.6±13.3
Gender (% men)	71.4%
ECG pattern (%)	
LBBB	52.4%
Intraventricular conduction delay	47.6%
Structural Heart Disease (%)	
Ischemic cardiomyopathy	52.4%
Dilated cardiomyopathy	38.1%
Valvular heart disease	9.5%
LVEF (%)	15.2±4.7
LVEDV (cm^3)	227.8±67.8
LVESV (cm^3)	191.8±62.1
MR severity (%)	
No MR	4.7%
Mild- mild to moderate	47.6%
Moderate	4.7%
Moderate to severe- severe	42.8%
Diastolic function	
Normal	0
Mild dysfunction	33.3%
Moderate dysfunction	42.8%
Severe dysfunction	23.8%
RV size	
Normal	57.1%
Mild/ mild to moderate enlargement	38.1%
Moderate enlargement	4.7%
Moderate to severe/ severe enlargement	0
RV function	
Normal	38.1%
Mild/ mild to moderate dysfunction	33.3%
Moderate dysfunction	23.8%
Moderate to severe/ severe dysfunction	4.7%
Aortic VTI (cm)	12.3±3.6
PAP (mmHg)	38.6±14.1

*Plus-minus values are means ± standard deviation.
MR: mitral regurgitation; Aortic VTI: aortic velocity time integral; PAP: pulmonary artery pressure.

At follow-up, 10 (48%) patients were considered responders according to the predefined criterion of ≥15% reduction in LVESV. Among the single tests, low-dose DSE (cut-off: 5%) and interventricular dyssynchrony provided the strongest prediction by exhibiting the highest positive likelihood ratio and the lowest negative likelihood ratio, respectively (Table III).

Table II. DTI and DSE results in participants at baseline before CRT

Test (cut-off value)	Mean ± SD	% ≥ Cut-off value
Doppler Tissue Imaging		
SLWMD (>60 msec)	53.3±28.8	28.6%
TS-diff (>100 msec)	90.5±30.2	33.3%
TS-SD (>33 msec)	34.7±12.8	57.1%
Interventricular mechanical delay (>40 msec)	50.5±19	66.7%
Dobutamine Stress Test		
LVEF increase (5-10 %)	5.5±3.3	29%
LVEF increase (>10 %)		14.2%

In contrast, the least predictive likelihood ratios belonged to septum-to-lateral wall delay and total asynchrony index. Therefore, we did exclude them from further combination calculations. Among the simultaneous tests, the application of all the three tests, namely low-dose DSE (cut-off: 5%), interventricular delay, and TS-diff, had the highest PLR, and a concurrent performing of low- dose DSE and inter-ventricular dyssynchrony provides the lowest NLR. We considered the tests above, using a cut-off value of 10% increase in LVEF for DSE. The latter results presented higher PLR for DSE (PLR of 5) with little change observed in NLR (Table V).Concurrent positive results of at least two of the three above-mentioned tests were also suitable in predicting the outcome, particularly for the cut-off point of 10% as compared to 5% (PLRs: 5 and 2.5, respectively).

Discussion

Major findings

The beneficial effects of CRT in terms of hemodynamic, clinical, and survival improvement have been largely documented.[2-4]

However, reports have shown that a substantial number of candidates for CRT device implantation according to current indications results in failure,[5] highlighting the importance of meticulous selection of suitable candidates.[1] Since the introduction of biventricular pacing, a number of parameters have been proposed as predictors of positive response after CRT, ranging from cardiac dyssynchrony assessment using electrical markers to directly studying mechanical dyssynchrony by means of DTI.[6, 8, 9, 16, 17]

Table III. Validity assessment of DSE (cut-off:5-10%), inter- and intraventricular dyssynchrony for prediction of response to CRT

Test	Sn	Sp	PPV	NPV	PLR (95%CI)	NLR (95%CI)
Single Test						
DSE	50	80	40	100	2.5 (0.7-9.3)	0.6 (0.3-1.5)
TS-diff	50	73.3	42.9	78.6	1.9 (0.6-6.1)	0.7 (0.4-1.3)
IVMD	83.3	46.7	38.5	87.5	1.6 (0.9-2.9)	0.4 (0.2-0.5)
SLWMD	33.3	73.3	33.3	73.3	1.2 (0.3-5.3)	0.9 (0.5-1.8)
TS-SD	50	40	25	66.7	0.8 (0.3-2)	1.3 (0.8-1.9)
Simultaneous Tests						
DSE- IVMD ‡	33.3	86.7	50	76.5	2.5 (0.4-14.5)	0.8 (0.2-2.5)
DSE –TS-diff‡	33.3	93.3	66.7	77.8	5 (0.5-47)	0.7 (0.1-4.4)
TS-diff - IVD ‡	33.3	93.3	66.7	77.8	5 (0.2-35.6)	0.7 (0.1-5.6)
DSE- IVMD –TS-diff‡	16.7	99	100	75	16.7 (0.07-3895)	0.8 (0.005-138)
DSE- IVMD †	99	40	40	100	1.7 (1.1-2.5)	0.03 (0.02-0.04)
DSE – TS-diff †	66.7	60	40	81.8	1.7 (0.7-4)	0.6 (0.4-0.8)
T S-diff - IVMD †	99	26.7	35.3	100	1.4 (0.7-7)	0.04 (0.2-0.9)
DSE- IVMD – TS-diff †	99	26.7	35.3	100	1.4 (1-1.9)	0.04 (0.02-0.07)
Positive test results (2/3)*	66.7	73.3	50	84.6	2.5 (0.9-7)	0.5 (0.2-0.9)

Table V. Validity assessment of DSE (cut-off: >10%), inter- and intraventricular dyssynchrony for prediction of response to CRT

Test	Sn	Sp	PPV	NPV	PLR (95%CI)	NLR (95%CI)
Single Test						
DSE	33.3	93.3	66.7	77.8	5 (0.5-47.1)	0.7 (0.1-4.5)
Simultaneous Tests						
DSE- IVMD ‡	16.7	99	100	75	16.7 (1.2-238.3)	0.8 (0.1-5.2)
DSE –TS-diff‡	16.7	93.3	50	73.7	2.5 (0.2-35.6)	0.9 (0.1-5.6)
DSE- IVMD –TS-diff‡	-	100	-	71.4	-	-
DSE- IVMD †	99	40	40	100	1.7 (1.1-2.5)	0.03 (0.02-0.04)
DSE – TS-diff †	66.7	73.3	50	84.6	2.5 (0.9-7)	0.5 (0.2-0.9)
DSE- IVMD – TS-diff †	99	26.7	35.3	100	1.4 (1-1.8)	0.04 (0.02-0.07)
Positive test results (2/3)*	66.7	86.7	66.7	86.7	5 (1.2-21.1)	0.4 (0.1-1.2)

Sn: sensitivity; Sp: specificity; PPV: positive predictive value; NPV: negative predictive value; PLR: positive likelihood ratio; NLR: negative likelihood ratio; DSE: low-dose dobutamine stress echocardiography; IVMD: interventricular mechanical dyssynchrony; TS-diff: the maximum difference in time to peak systolic velocities (TS) in two segments among 12 segments; SLWMD: septum to lateral wall mechanical delay. ‡ denotes that the overall test result is positive if the entire mentioned tests exhibit positive results and is negative if at least one of them is negative. † denotes that the overall test result is positive if at least one of the mentioned test exhibits positive result and is negative if all of them are negative. * denotes that the overall test result is positive if at least two out of the three tests (DSE, IVMD and TS-diff) have positive results.

To date, there is no gold standard test or criteria for the identification of potential responders to CRT before the implantation of the pacemaker.[1,16] Recent studies have presented myocardial viability and contractile reserve as an independent predictor of responsiveness.[11,14,15] However, data regarding concurrent assessment of potential predictors are lacking. This prospective study is the first to address the validity of the current predictors of CRT altogether. The main findings of the present study can be summarized as follows: 1) among single parameters, positive results of low-dose DSE and negative results of interventricular dyssynchrony assessment have the highest predictive powers, and 2) in simultaneous testing, positive results of all the three tests (DSE, interventricular dyssynchrony, and TS-diff) and negative results of both DSE and interventricular dyssynchrony provide the strongest prediction.

Role of single tests in predicting responders to CRT

When performed singly, DSE (with either cut-off values) had the highest PLR, which means that patients with positive response will more probably benefit from CRT; and interventricular dyssynchrony had the lowest NLR, which denotes that implantation will not be beneficial for patients without it.[18] These results are also explicable in terms of sensitivity and specificity.[18,19] DSE has the highest specificity, which means patients with positive results are predictive and interventricular dyssynchrony had the highest sensitivity. The least predictive single tests were septum-to-lateral wall mechanical delay and total asynchrony index, which had LRs near 1.

Low-dose DSE is a valuable test for detecting myocardial viability and contractile reserve.[12,13] Contractile reserve assessed by DSE is an independent predictor of response to CRT.[14] In fact, CRT will be efficient if there is a sufficient amount of viable myocardium with sufficient contractile reserve, so the assessment of viability is necessary before device implantation.[11,14] Advanced heart failure with massive myocardial fibrosis and loss of contractile reserve, even in the presence of severe mechanical dyssynchrony, can lead to failure of implantation response.[11] Moreover, DSE provides prognostic information in terms of survival.[15]

With a cut-off level of 5% increase in LVEF during low-dose DSE for predicting acute response to CRT (defined as a reduction in LVESV $\geq$ 15%), we obtained a sensitivity of 50% and specificity of 80%. We analyzed the results with the cut-off value of 10%. This analysis yields a higher PLR, which emphasizes the role of myocardial contractile reserve extent for the chance of responsiveness. Nevertheless, a sensitivity of 76% and specificity of 87% have been shown previously for detecting the same outcome at six months' follow-up, using the same cut-off level.[14]

Our study demonstrated that interventricular dyssynchrony serves as a valuable test, especially for excluding potential non-responders. Similarly, the effective role of interventricular dyssynchrony has been shown in a previous study.[17] Intraventricular dyssynchrony was assessed by three parameters in this study: Septum-to-lateral wall mechanical delay and total asynchrony index had the least predictive role in identifying early responders to CRT based on echocardiographic indices. Septum-to-lateral wall mechanical delay evaluated by pulse-wave DTI has previously failed to have a predictive role in identifying responders to CRT.[20]

Role of simultaneous tests in predicting responders to CRT

When carried out simultaneously, positive response in all the three tests had the strongest predictive value for the inclusion of the patient with PLR of 16.[7] In addition, although negative results achieved just from DSE can not be suggestive of response failure following DSE, when it is concurrent with lack of interventricular dyssynchrony it will highly suggest implantation will be a vain attempt. This finding is consistent with previous studies.

Study advantages and limitations

The present study is the first to examine the validity of a variety of tests together in order to obtain the most accurate criteria for prospective prediction of CHF patients' response to CRT and it thus provides insight into the inclusion and exclusion of potential responders and non-responders, respectively. Furthermore, the current study offers the first evidence-based approach to the prediction of responders to CRT by using likelihood ratios, which can provide a dynamic interpretation of a series of tests and can estimate a given outcome using pretest probabilities.[19,21] However, our study suffers from a few limitations. Firstly, the total number of patients evaluated in the current study is small, which has led to wider confidence intervals for LRs. Secondly, although we are following these patients for assessing long-term outcome, the present result represents the early response (observed three days after implantation) to CRT. It was shown previously that LVEF improvement peaks at 6-12 months following CRT.[22] Finally, in this study the criterion defining the response to CRT was based on LVESV changes and did not consider clinical outcomes. Be that as it may, the results of a former study revealed that early echocardiographic improvements can predict late clinical responsiveness to CRT.[10]

Conclusion

Our results demonstrate that the strongest single predictor of acute response to CRT is inotropic contractile reserve assessed by low-dose DSE. When positive results of low-dose DSE are accompanied by inter- and intraventricular dyssynchrony (TS-diff), the most accurate prediction of acute response to CRT can be achieved.

Conflict of Interest

No conflicts of interest have been claimed by the authors.

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